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By Chin Kuo-chang, Tsou Kang, et al.

- COMMUNIST CHINA -

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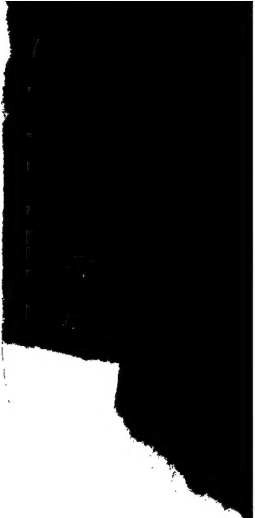
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FOREWORD

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STUDIES ON THE PHARMACOLOGICAL ACTIONS OF CORYDALIS

VI. Effects of Corydalis B on the Central Nervous System

- COMMUNIST CHINA -

Following is a translation of an article written by Chin Kuo-chang (金國章), Tsou Kang (鄒岡), Tang Hsi-ts'an (唐希燦), Ch'en Jui-t'ing (陳瑞女亭) and Hsu Pin (許彬) of the Institute of Materia Medica, Academia Sinica, Shanghai, in Sheng-li Hsueh-pao (Acta Physiologica Sinica), Peiping, Vol 24, No 2, June 1960, pages 110-120.⁷

Detailed information on the chemical properties of the Chinese drug corydalis ambigua has been made available. (1,2) Numbers in parentheses refer to bibliographical entries⁷. The writers of this paper have made some studies on the pharmacological actions of this drug and have proved that its derivative di-tetrahydropalmate (see Fig 1), simplified as corydalis B, has good analgesic properties (3), does not easily yield to tolerance (4), has very low toxicity, and is safer than other analgesic drugs commonly used. (6,7) Clinical tests have also proven that corydalis B has good analgesic properties (8-11), giving satisfactory results when used for relieving pain in tumors and in uterine contraction following delivery. In the process of our experiments we found that corydalis B has a definite tranquilizing effect on monkeys. (7) These pharmacological actions of the drug have possible clinical applications, and should be given further investigation. Moreover, to understand more fully the characteristics of the actions of corydalis B, we must carefully analyze these actions with respect to their effect on the central nervous system. This paper is a report on the results of our studies of this particular aspect.

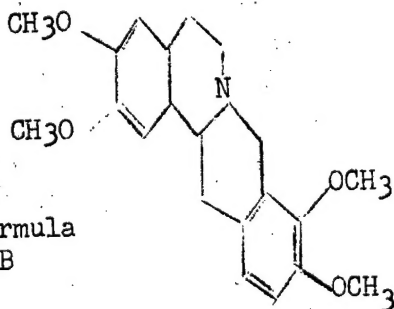


Fig. 1. Structural Formula of Corydalis B

Method and Results of Experiments

The corydalis B used in this experiment was in crystalline form, with sulphuric acid as the menstruum. It had been prepared by the Chinese Drug Department of this institute. Its melting point is 218-220°C. It is soluble in water, and may be used hypodermically.

I. The Calming and Tranquilizing Actions of Corydalis B and an Analysis Thereof

Effect of Corydalis B on Length of Sleep Induced by Barbital

White mice were used in the experiment. Intraperitoneal injection of hexobarbital sodium, 100 mg/kg, was first administered to the animals to induce sleep. The lapse of time between the disappearance of reflex and the reappearance of reflex was considered to be the length of the sleep period. Room temperature was maintained at 23-25°C.

Thirty white mice were selected and divided into three groups. The first group was given hexobarbital sodium by intraperitoneal injection and was to be used for comparative observations (control group). The average length of the sleep period the animals underwent was 37 ± 1.05 minutes (95% confidence limits). The second group was given corydalis B by intraperitoneal injection, 20 mg/kg. 30 minutes later the animals were given hexobarbital sodium by injection. The length of the sleep period averaged 73 ± 1.89 , which is about twice as long as that of the control group. The difference is prominent ($P < 0.05$). The third group was first given corydalis B orally, 40 mg/kg; 40 minutes later hexobarbital sodium was injected into them. The average length of the sleep period was 147 ± 8.41 minutes, which is more than three times that of the control group. The difference is unusually prominent ($P < 0.01$). When the drug administered orally was increased to twice the dosage administered intraperitoneally, the length of the sleep period correspondently increased twofold.

220 other white mice were selected, 40 of whom were given hexobarbital sodium by intraperitoneal injection and were used as control; the rest were divided into six groups and were given corydalis B by intraperitoneal injection, 40 mg/kg. Then 10, 40, 70, 130, 190, and 250 minutes respectively after the intraperitoneal injection of corydalis B, hexobarbital sodium was again given them hypodermically. The prolonged length of the sleep period induced by the drug in each of the animals appears in Table I. The length of sleep extended by the action of hexobarbital sodium -- 10 and 40 minutes, respectively -- following injection of corydalis B are comparatively close, in either case it being about three times that of the control group. The difference is very prominent ($P < 0.01$). The extended length of the sleep periods brought about by hexobarbital sodium -- 70 and 130 minutes, respectively -- following injection of corydalis B in both cases are about two times that of the

control group. The different is also prominent ($P < 0.01$), though the action was shorter than that of the first two groups. But for 190 and 250 minutes, respectively, following injection of corydalis B, the hexobarbital sleep was prolonged somewhat. However, the difference is not very prominent ($P > 0.05$). These last two groups are closer to the control group with respect to action time.

Table I

Intraperitoneal Injection of Corydalis B, 40 mg/kg,
Synergetic Action with Hexobarbital

Minutes After Injection of Corydalis B	Number of White Mice	Average Length of Sleep (in minutes) (95% confidence limits	Compared with Control Group	
			Length of Sleep Prolonged (%)	P Value
10	30	134 ± 22	235	< 0.01
40	30	121 ± 19	220	< 0.01
70	30	84 ± 16	110	< 0.01
130	30	89 ± 15	122	< 0.01
190	30	47 ± 10	17	> 0.05
250	30	47 ± 7	12	> 0.05
Control Group	40	40 ± 5	0	

2. Effect of Corydalis B on Passive Activity of Mice

(a) Revolving cage -- The speed of the revolving cage had been adjusted to one revolution per 40 seconds, at a tilting angle of 60° when in motion. (12) The 40 mice were divided into four groups. Forty minutes after intraperitoneal injection of corydalis B, observation of the behavior of the animals in the cage was made for 30 minutes. The lapse of time until the individual animals lost their foothold and fell and the percentage of such falls were recorded.

Then, 10-20 minutes after drug administration, those given a comparatively higher dosage showed signs of excitant behavior: external stimulation caused them to jump, but after a while their activities diminished; they became quiet, or closed their eyes and remained still. When the animals were placed in the revolving cage for experimentation, they were evenly distributed, so that the individual animals could move from their original positions with ease when necessary to more favorable positions for counteraction to the earth's gravitation. A few minutes after the cage had been set in motion, a majority of the animals held tight

to the screen of the cage with their claws, closed their eyes, and stopped changing their respective positions. By means of a computer it was determined that the effective dosage (ED₅₀) for the fallen animals was 29.7 mg/kg.

(b) Rotorod -- A wooden rod, 2.5 mm in diameter (13,14) was attached stationary to a rotary disk. There were 18 sections on the rod. The mice were placed on the rod. When the rod started to rotate the animals were made to move in the opposite direction of the rotation of the rod. The speed of the rotorod was set at 15 rotations per minute. The experiment lasted 30 minutes. Observations were made of the percentage of animals that dropped off the rod. A total of 50 white mice divided into five groups were used. Forty minutes following intraperitoneal injection of corydalis B they were subjected to the above mentioned experiment on passive activity. As time went by the animals gradually lost their equilibrium, and the number dropping off the rotorod gradually increased. The effective dosage of corydalis B was found to be 27 mg/kg for half the number [sic].

3. Effect of Corydalis B on the Spontaneous Activity of Mice

This phase of the experiment involved the application of photo-electric devices. (14, 15) A computer was used to register the spontaneous activity of the animals for 30 minutes. The cage was comfortable and quiet; room temperature was 22-25°C. Uniform conditions were maintained as close as possible in the experiment conducted by the different teams. Observations were made of the activity of the drugged group and the control group at the same time and for the same length of time. There were five animals in each group. The registered result of each group represents the total numerical value of the activity of the animals of the group. The dosage of intraperitoneal injection of amphetamine was 4 mg/kg. Thirty minutes following injection the animals were placed in the photo-electric device for observation. The control group was given saline solution by intraperitoneal injection. The excitant behavior of the spontaneous activity of the 30 mice (6 groups) following intraperitoneal injection of amphetamine was 600 ± 8.02 movements, 95% confidence limits, compared with 231 ± 4.66 of the saline solution control group. This is an increase of more than two times. The difference between the two is prominent ($P < 0.05$). See Table II.

Another group of 30 mice was given corydalis B by intraperitoneal injection, 40 mg/kg. When they were given amphetamine hypodermically 30 minutes afterward their excitant activity (46 ± 1.06) not only was not increased but was even noticeably less than that of the saline solution control group, ($P < 0.05$). If compared with the group that had received amphetamine injection alone, that is, compared with spontaneous activity on the basis of excitant behavior, the difference between the two would be extraordinarily prominent ($P < 0.01$). It is evident, therefore, that corydalis B not only counteracts amphetamine but directly reduces the excitant activity of the mice.

Table II

Effect of Corydalis B on Excitant Activity Induced by Amphetamine
(Drugs injected intraperitoneally)

Drug or Chemical Used (mg/kg)	Number of Mice Used	Number of Times of Activity (95% reliable)	Compared with Saline Solu- tion Group (P value)	Compared With Amphetamine Group (P Value)
Corydalis B + Amphetamine (40 + 4)	30	46 ± 1.06	< 0.05	< 0.01
Amphetamine (4)	30	600 ± 8.02	< 0.05	
Saline Solution	30	231 ± 4.66		

3. Effect of Corydalis B on the Toxicity of Amphetamine

A number of healthy male white mice were selected and were placed 5 to a cage. (16, 17) These were to be used as control. The experiment was conducted at room temperature, 25°C. Ten animals in the control group were given amphetamine by intraperitoneal injection, 20 mg/kg. Ten minutes following the injection the animals exhibited, unusual excitant behavior, attacking one another and shrilling. All died within six hours. Fifty other mice, divided into five groups, ten animals to the group, were given corydalis B in different dosages by intraperitoneal injection, one hour following which they were given amphetamine, 20 mg/kg. It was found that corydalis B had protective action, counteracting the toxicity of amphetamine on the mice, preventing the latter from dying of toxicity. Such counter-acting action was in direct proportion to the dosage of corydalis B given. It was determined that the ED₅₀ (effective dosage of corydalis B in preventing half of the animals from dying) was 32.1 ± 0.09 mg/kg (95% confidence limits). See Table III.

Table III

Counteraction of Corydalis B on Toxicity of Amphetamine
(Intraperitoneal Injection of amphetamine was administered one hour
following intraperitoneal injection of corydalis B)

Corydalis B (mg/kg)	Amphetamine (mg/kg)	Number of Mice Used	Number of Mice Died
0	20	10	10
20	20	10	8
28	20	10	5

Table III Continued

Corydalis B (mg/kg)	Amphetamine (mg/kg)	Number of Mice Used	Number of Mice Died
39.2	20	10	4
55	20	10	2
77	20	10	0

ED₅₀ = 32.1 ± 0.09 mg/kg (95% confidence limits)

5. Effect of Corydalis B on the Motor Defense Conditioned Reflexes in Cats

The method employed in this phase of the experiment was based on that of Brady, et al. (18). A special wooden box constructed with two small chambers connected by a door was used. The floors of the two chambers were copper plates and could be electrically stimulated independently. On the front side of the box there was a glass window through which one could observe the inside. An electric bell was installed on top of the box for conditioned reflex stimulation. Within five minutes following the ringing of the electric bell the cat in the box had to run to the chamber other than the one it was placed in, otherwise it would be electrically stimulated. It was so arranged that the cat had to complete its running to the other chamber within ten seconds. Fifteen conditioned stimulations were given in each process at 30-second intervals. Observations were made of the latent periods and the disappearance of the conditioned reflex. The disappearance percentage of the conditioned reflex was also recorded. As a rule, the experiment was started 30, 60, 90, and 120 minutes respectively following administering of drugs.

Two cats went through the experiment 8 times in all, two times of which the animals were given corydalis B by intraperitoneal injection. Six times they were given drug by subcutaneous injection (30 mg/kg 3 times; 10, 20, 40 mg/kg 1 time each). Within 20-30 minutes following drug injection the cats exhibited excitant behavior (pupils of eyes wide open, growling, jumping, nausea, emesis, etc.), which condition persisted 20-40 minutes. They then became quiet and appeared drowsy. Thirty minutes following introduction of drug by subcutaneous injection, 30 mg/kg, reflex was noticeably affected, at first the delay period became shorter, followed by disappearance of conditioned reflex, and finally by the disappearance of unconditioned reflex.

At this time the animals appeared excitant: they growled and jumped around. This condition was most noticeable 50-90 minutes following drug introduction. After that the animals quieted down, and the disappearance of conditioned reflex and unconditioned reflex was comparatively higher in percentage. (See Table IV) Then, 2-3 hours later the action of corydalis B gradually wore off, and the activity of conditioned reflex was

Table IV

The effect of Corydalis B Injected Subcutaneously into Cats,
30 mg/kg, on the Animals Defensive Conditioned Reflex

Cat No.	Exp'ment No.	Experiment Time (minutes)	Average Delay Period of Conditioned Reflex	Disappearance of Conditioned Reflex (%)	Disappearance of Unconditioned Reflex (%)	External Changes
1	3	before drug adminis.	2.4	7	0	growled, not calm calm
		30 after drug adminis.	3.4	6	28	
		60 after drug adminis.	-	100	100	
		120 after drug adminis.	3.6	7	0	
1	4	before drug adminis.	4.4	0	0	growled, lay down and would not move ditto
		30 after drug adminis.	3.0	87	47	
		60 after drug adminis.	-	100	94	
		90 after drug adminis.	-	100	100	
		120 after drug adminis.	4.2	13	0	
2	5	before drug adminis.	2.8	7	0	excitant behavior rather short calm ditto
		30 after drug adminis.	3.2	47	0	
		60 after drug adminis.	4.5	80	0	
		90 after drug adminis.	4.5	87	7	
		120 after drug adminis.	4.2	53	0	
		180 after drug adminis.	3.1	0	0	

gradually restored. The delay period was still rather long. In a small number of cases the condition of reflex disappearance still existed. But 24 hours later, however, conditioned reflex almost completely reappeared. When the drug was given by intraperitoneal injection, 10 mg/kg, the above-mentioned comparatively weak effect was apparent. But when the dosage was increased to 40 mg/kg, given either subcutaneously or by intraperitoneal injection, the effect with respect to conditioned reflex was basically the same as that produced by dosage of 30 mg/kg. When the drug was administered subcutaneously, 10-20 mg/kg, the delay period was prolonged, but there was no disappearance of conditioned reflex.

6. Effect of Corydalis B on Apparent Activity When Injected Into Cranial Cavity of Cat

In accordance with the Feldberg and Serwood method, tubing was introduced into the cranial cavity of the cat. In our experiment plastic tubing was used. The experiment was started five days after the surgical operation had been completed. Observations were made four times on three cats. Corydalis B was dissolved in sterilized distilled water, the concentration being 10 mg/ml and 40 mg/ml, respectively, in two different batches. Following injection of 1 mg corydalis B (0.1 ml solution) into cats No. 1 and No. 2, the animals lay low and would not move. Within 10-15 minutes they became drowsy and even snored. They could be awakened by external stimuli, but would continue to sleep if stimuli were removed. This drowsy condition persisted for two hours. In the process nausea was observed on three or four occasions.

Cat no. 3: This animal originally showed signs of fear, and subsequently attempted escape several times. But following intraperitoneal injection of 1 mg (0.02 ml solution) of corydalis B, signs of fear diminished, but the animal exhibited drowsiness that the other two cats exhibited. After three days, a second experiment was performed on cat no. 3. Prior to the administration of the drug the animal still exhibited signs of fear, but 10 minutes after 2 mg of corydalis B (0.05 ml solution) had been given the animal, it no longer made any attempt to escape, but doubled up, closed its eyes and went to sleep. It could not be awoken by external stimuli. This condition persisted for two hours.

7. Effect of Corydalis B on Electroencephalogram of Rabbit

Rabbits weighing 2.5-3.5 kg were used in this experiment. Silver wire was used in making the electrodes for registering the electric waves emanated from the motor and sensory areas of the cortex and the occipital lobe of the animal's brain. The method employed is the same as that reported in literature bearing on the subject. The animal was placed in a specially built wooden box, its head being exposed. A 10% procaine solution (containing a small amount of adrenalin) was injected subcutaneously into the top of the head as local anaesthesia. An incision was made of the scalp. A small hole was made in the skull by means of a drill equipped with a bit

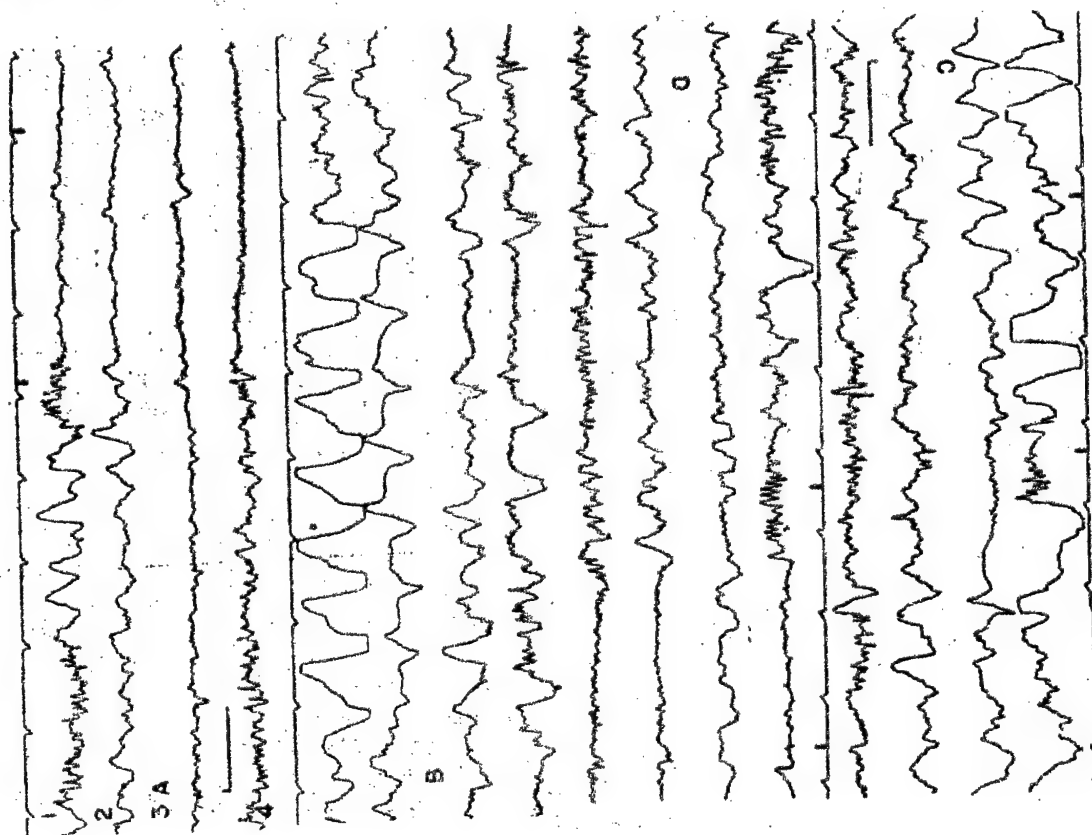
made of bone to keep the electrodes secure. The experiment was conducted in an adjoining room. The brain waves were recorded by means of an electroencephalograph. Corydalis B was injected slowly, 15 or 20 mg/kg, into the vein near the edge of the animal's ear. Morphine was injected, 5 mg/kg, into other rabbits to be used as the control group. In a great majority of the cases electrical stimuli furnished by induction coil were applied to the forelimbs of the animal for 5-10 seconds to see the effect of corydalis B. The result: the brain waves had the characteristics of reactions such as being aroused. In addition, in a small number of cases, electrocardiograph studies were made of the animals.

Fourteen other rabbits were given corydalis B: half of the animals received 15 mg/kg, the other half 20 mg/kg. Prior to drug administration their brain waves were mainly fast ones and of low voltage (16-24 c/s, 25-75 μ v). Emanating from the motor sensory areas sometimes were shuttle-shape waves (12-14 c/s, 50-250 μ v), from the occipital lobe sometimes α -waves (Fig 2 A). The waves of three of the rabbits were of the multiple type: some were low voltage fast waves, some medium slow waves (8-16 c/s, 150-200 μ v), and some were shuttle-shape waves. Those from the occipital lobe were α -waves). Following application of electrical stimuli, the frequency of the brain waves was raised, the vibration field was reduced, showing reaction resembling that of being aroused. This action persisted for 20-40 seconds (Fig 2A).

Then, 2-5 minutes following injection of corydalis B, changes in the brain waves were observed. Low voltage fast waves were reduced. Slow waves emanated often from the motor sensory areas, some also from the occipital lobe, though less often. Three to seven minutes following drug administration, action was most noticeable. Slow waves, instead of low voltage fast waves, were observed. The most noticeable were those from the motor sensory areas. They were principally high voltage slow waves (1.5-3 c/s, 250-400 μ v) sometimes accompanied by shuttle-shape high voltage fast waves (12-14 c/s, 200-300 μ v). (See Fig 2 B). The changes of the electric waves which emanated from the occipital lobe very often were not as prominent as those which emanated from the frontal lobe, the most prominent being those emanated from the central lobe. In general, most were slow waves. This action lasted 5-15 minutes (about 5-25 minutes following administration of drug). Now reaction to electrical stimuli disappeared (Fig 2 C). Sometimes while those which emanated from the motor sensory areas were still slow waves, those from the occipital lobe became fast waves. The afteraction of reaction to stimuli was also noticeably shortened. Thereafter the effect of corydalis on the brain waves gradually disappeared. The vibration field of slow waves was first reduced. This was followed by a reappearance of fast waves. The duration of afteraction of reaction to electrical stimuli was lengthened and the transition from fast waves to slow waves continued for 30-60 minutes (generally 40 minutes), following which the brain waves became normal again (Fig 2 D).

Apparently following injection of corydalis B, 20 mg/kg, the rabbits closed their eyes, became calm, exhibiting a sleeping condition. Characteristic were the high voltage slow-brain waves. In the process of

Fig. 2. Electroencephalogram showing effect of corydalis B on the brain waves of rabbit. A, B, C, and D are records of observations taken 7, 12, and 30 minutes before and following administration of drug, respectively (intravenous injection, 20 mg/kg). — represents 50 μ V/1 sec; 1, 2, 3, and 4 represent waves coming from the cortex evoked by 4 electrodes: 1, electrode 3-4 mm in front of hat-shape fissure; 2, electrode on hat-shape fissure; 3, electrode 2-3 mm behind hat-shape fissure; 4, on occipital lobe. The first three represent motor and sensory areas of cortex. Over 1 are time intervals and stimulation marks. A, C, and D all indicate that skin had been stimulated 3 seconds. Before drug administration (A) electrical stimuli evoked reaction (aroused), which lasted 15 seconds; 7 minutes following drug administration (B), action was most noticeable. Twelve minutes following drug administration (C), reaction to electrical stimuli disappeared. Thirty minutes following drug administration (D) brain waves were close to normal: electrical stimuli evoked some reaction.



recovery the rabbits opened their eyes, and the transition from fast waves to slow waves was usually evident. Following injection of corydalis B, 15 mg/kg, the action was similar to what happened when the drug in dosage of 20 mg/kg was given, but the duration of action was comparatively shorter. In general, the action was most prominent 10-15 minutes following administration of the drug, and recovery was complete in 20-30 minutes.

In other six rabbits the normal brain waves were principally low voltage fast waves. Following intravenous injection of morphine, 5 mg/kg, it was observed that the action was characteristically the same as that evoked by corydalis B. Emanating from the motor sensory areas and the occipital lobe were slow waves and high voltage slow waves. The action on the brain waves was most prominent 10-30 minutes following drug administration. Recovery was effected in 30-90 minutes.

II. Dosage of Corydalis B for Counteracting Convulsion and its Action on Electric Shock

1. LD₅₀ of Intraperitoneal Injection of Corydalis B

For seven consecutive days 278 healthy white mice were selected and were experimented on at four different times to determine the LD₅₀ of corydalis B for them. These animals were given the drug by intraperitoneal injection, 466-1210 mg/kg. Within 10-39 minutes the animals exhibited some excitant behavior -- jumping, which was inhibited after a while. Then the animals closed their eyes and lay prostrate, motionless. Their respiration slowed down; when touched they still reacted by wagging their tails. Those that received comparatively high doses died within 1-2 days, the rest recovered within seven days. Computation determined that the LD₅₀ was 754 mg/kg.

2. Effect of Corydalis B on Strychnine Convulsions and Metrazol Convulsions

One group of 40 and another group of 55 white mice were selected, and were given strychnine and metrazol, respectively, by intraperitoneal injection to produce convulsions. For the strychnine type, strong and continuous convulsions were indicated; for the metrazol type intermittent convulsions were indicated. (21) It was found the ED₅₀ for strychnine convulsions and metrazol convulsions was 130 ± 0.09 , 5.15 ± 0.32 mg/kg respectively.

Independently, two groups of white mice, 60 in one group and 45 in the other, were selected and given corydalis B, 90 mg/kg, by intraperitoneal injection. One hour following that the two groups were given strychnine and metrazol, respectively. Observations were made of the conditions of their convulsions. It was determined that the ED₅₀ for the two groups was 0.708 ± 0.015 and 64.5 ± 0.014 mg/kg, respectively. After corydalis B injection, the ED₅₀ of strychnine was reduced. When this was compared with the results obtained from animals who were not given corydalis

B, the difference was very prominent ($P < 0.01$). This demonstrates that corydalis B reinforces the convulsion-producing action of strychnine. The fact that injection of corydalis B increased the ED₅₀ of metrazol, and the fact that the difference between this group and the group that had not been given corydalis B is unusually prominent ($P < 0.01$) demonstrate that corydalis B exercises inhibiting action on metrazol convulsions.

3. Experiment on the Counteraction of Corydalis B on Electric Shock

Seventy five white mice were selected, their body weight ranging from 20 to 25 grams, for experiments with electric shock. (22) A current of 12.5 amperes was made to pass through the two ears of the animal within 0.2 second to produce convulsions. When the animals were given corydalis B, 90-100 mg/kg, by intraperitoneal injection there was no counteraction to electric shock, but when the dosage was increased to 150-300 mg/kg, there was partial counteraction. When the dosage was 100 mg/kg, it had syngetic action with phenytoin, and could render the latter, in effective dosage, effective in counteracting electric shock. (See Table V).

Table V

Effect of Corydalis B on Electric Shock in White Mice

Drug (intraperitoneal injection)	Dosage (mg/kg)	Number of Mice	Effectiveness in counteracting Electric Shock
Corydalis B	90-100	20	0
	150	10	30
	200	25	56
Phenytoin	7.5	10	0
	10		30
	100 + 7.5	10	40
Corydalis B + Phenytoin	100 + 10	10	50
	150 + 10	10	60

III. Action of Corydalis B on Emesis

1. Effect of Corydalis B on Emesis Induced by Apomorphine

Some healthy dogs were selected into whose bodies was injected

apomorphine, 0.1, 0.2 mg/kg, subcutaneously to induce emesis. Other selected dogs were given corydalis B subcutaneously, 40 mg/kg, one hour following which apomorphine was injected. Then the two groups were subjected to "cross experiment." Each animal was observed two times at seven day intervals. When emesis was evoked under the same conditions, each dog was a control group animal and at the same time a drugged group animal. Four dogs were given apomorphine by subcutaneous injection, 0.1 mg/kg. In three of the animals emesis was evoked, but when the dosage was increased to 0.2 mg/kg emesis was evoked in all four dogs. One hour following subcutaneous injection of corydalis B, 40 mg/kg, the emesis-evoking action of apomorphine was counteracted in the animals who had been given the apomorphine, 0.1, 0.2 mg/kg, respectively. Of six other dogs, three had emesis following subcutaneous injection of apomorphine 1 mg/kg. The remaining three were first given corydalis B, 40 mg/kg, and an hour later apomorphine was injected into them. There was still emetic action. This indicates that corydalis B has no counteraction of the emesis-inducing action of apomorphine in a 1 mg/kg dose.

2. Effect of Corydalis B on Emesis Induced by Copper Sulphate

Twelve healthy dogs were selected for this experiment. To six of these animals copper sulphate solution was administered by way of the digestive tract, 20 mg or 100 mg/kg, to induce emesis. The other six animals were first given corydalis B, 40 mg/kg, by subcutaneous injection. An hour later they were given copper sulphate solution orally. A few minutes following the administration of copper sulphate solution, 20 mg or 100 mg/kg, the animals in the control group exhibited emetic action. The muscles in the adominal region contracted violently, and within 6-8 minutes emesis occurred five times connecutively. All the animals who had been first given corydalis B and then copper sulphate exhibited emetic action, showing no appreciable difference between them and the control group, both with respect to the delay periods of emesis (4-11 minutes) and the number of occurrences of emesis.

In the experiment on emesis stated above, when corydalis B was injected subcutaneously into the dogs, 40 mg/kg, it produced a definite tranquilizing effect in every case. The animals crouched, closed their eyes, and were drowsy, but they still reacted to external stimuli, and when gently pushed, they would open their eyes wide and then stand up. This manifestation of tranquility could persist for 2-5 hours.

IV. Hypothermic Action of Corydalis B

Seventeen white rats, weighing 90-120 grams each, were used in this experiment. Room temperature was maintained at 20°C. The rectal temperature of each animal was taken and recorded three times a day at one-hour intervals for two consecutive days. Their average body temperature was $38.74 \pm 0.4^{\circ}\text{C}$. On the third day corydalis B was given the animals

by subcutaneous injection, 80 mg/kg; 1, 1.5, 2.5 hours following injection, respectively, their respective body temperatures were taken, the average of which was $37.5 \pm 0.4^{\circ}\text{C}$. This was a drop of more than 1.10°C , compared with the temperature taken before drug administration. On the second day following drug administration body temperature of the animals was again taken. It was found to be $38.9 \pm 0.5^{\circ}\text{C}$ on the average, which is, for all practical purposes, the same as what it was before the administration of the drug. Following the injection of corydalis B all the animals exhibited tranquility. Activities such as jumping, running and making noises decreased.

Discussion

In the process of our studies of corydalis B we discovered that this drug has calming action and properties similar to those possessed by tranquilizers. We subsequently made a comparatively thorough study of this aspect of the drug. Based on the lengthening of barbitol sleep and the passive activity and spontaneous activity of white mice, it has been clearly demonstrated that corydalis B has tranquilizing properties. In other experiments performed on white rats and dogs, the tranquilizing action of corydalis B has been confirmed. In the experiment on the cerebral cortex of rabbits by means of electroencephalograph, corydalis B, in effective anaesthetic dosage, brought apparent calmness to the animals, caused the brain waves of the rabbits to change into high voltage slow waves, which are characteristics of the brain in the tranquil state. Clinical tests of corydalis B showed that patients given this drug slept lightly, were easily aroused, and had fewer dreams in their sleep. (8) All these facts prove that corydalis B has good tranquilizing action. When a minute quantity of this drug was injected into the cranial cavity of a cat, it produced a tranquilizing and hypnotic effect, showing that it served as a mechanism regulating the central nervous system. Drugs for treating mental illness usually have tranquilizing action, (23, 24) e.g., reserpine (25) and other alkaloids of rauwolfia serpentina (26) Whether or not corydalis B has tranquilizing properties is a question that is worth studying. In the experiment on monkeys corydalis B was found to counteract the toxicity of amphetamine. In the experiment on conditioned reflex it demonstrated properties similar to those of tranquilizers; it proved to have a certain calming action on fierce monkeys (7). In the studies of brain waves by means of electroencephalograph it was shown that corydalis B could inhibit the activity of the brain stem. (27) All these facts demonstrate that corydalis B has some of the properties that are characteristic to tranquilizers. But whether or not it can lend itself to the effective treatment of mental illness remains to be determined by clinical tests.

When injected into cats intraperitoneally, corydalis B made the animals restless and prompted aggressive behavior such as hissing before it finally tranquilized them. Morphine has a similar effect. (28) Corydalis B reinforces the exciting effect of strychnine, thus reducing

the latter's convulsion threshold. It has been inferred that corydalis B excites the spinal fluid, being similar to morphine in this respect. (29) But corydalis B is unlike morphine in that it does not evoke the straub reaction in white mice as does morphine. Corydalis B is different from morphine in other respects: its tolerance is not plain; it is not habit-forming; it does not suppress urination or respiration; it induces light sleep, and does not induce many dreams. (8) All these are advantages possessed by corydalis B. In the experiment on emesis inducement it was proved that this drug inhibits emesis at the central nervous system level.

Based on the information available, corydalis B has the anaesthetic properties of morphine, but at the same time it possesses some of the properties of tranquilizers. Its chemical structural formula is different from those of ordinary tranquilizers. From this point of view it may be said that corydalis B is a new type of drug. The relationship between its structural formula and its curative effectiveness is worth further studies.

In the experiment on delay periods of barbitol sleep it was learned that equal amounts of corydalis B administered differently, i.e., orally and by intraperitoneal injection, produced practically the same results in both ways of administration with respect to length of the sleep period. The way of drug administration being constant, there was a relation between the dosage of corydalis B and the length of the sleep period. We may infer that the condition of corydalis B absorption in the digestive system is good. Table I shows that the synergetic action of corydalis B with sodium barbitol is strongest within 40 minutes following administration and that it becomes weaker within 70-130 minutes, unnoticeable within 190-250 minutes. Table I helps explain the delay period of action of corydalis B.

Summary

1. Corydalis B has synergetic action with hexobarbital sodium reduced passive and spontaneous activity in white mice, counteracted hyperactivity induced by small doses of amphetamine. The effective dosage was 20-40 mg/kg.

Administration of corydalis B by subcutaneous injection, 10-30 mg/kg, to cats first induced hyperactivity, then inhibition. Larger doses inhibited both conditioned reflex and unconditioned reflex, the delay period being 2-3 hours or longer -- similar to results induced by the drug by intraperitoneal injection. Injection of corydalis B into the cranial cavity of cats from the side abolished fear and the impulse to escape and induced drowsy behavior. The cats could easily be aroused by external stimuli.

Normally the brain waves of the cerebral cortex are of the low voltage fast variety. Intravenous injection of corydalis B, 15-20 mg/kg, caused the brain waves to change to the high voltage slow variety. At such times induction coil stimulation of the skin produces no noticeable waking behavior. After a lapse of 40 minutes the action of corydalis B disappeared.

2. *Corydalis* B aggravated strychnine convulsions, but inhibited metrazol convulsions. It had some synergetic action with phenytoin.
3. *Corydalis* B tranquilized the central nervous system and produced a slight hypothermia.

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